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Filed: July 20, 2001

**AMENDMENT AND RESPONSE TO OFFICE ACTION****Remarks**

Claims 1-4 and 6-10 are pending. Withdrawal of the rejection under 35 U.S.C. § 112, second paragraph, is appreciated.

**Rejection Under 35 U.S.C. § 112, first paragraph (written description)**

Claims 1-4 and 6-10 were rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor had possession of the claimed invention. Applicant respectfully traverses this rejection to the extent that it is applied to the claims as amended.

**Legal Standard**

"There is a strong presumption that an adequate written description of the claimed invention is present in the specification as filed". *Wertheim*, 541 F.2d at 262, 191 USPQ at 96 (CCPA 1976). The written description requirement for a claimed genus may be satisfied through a sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or a disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus (see i)(C), above). See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus when there is substantial variation within

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the genus, one must describe a sufficient variety of species to reflect the variation within the genus. On the other hand, there may be a situation where one species adequately supports a genus. See, e.g., *Rasmussen*, 650 F.2d at 1214, 211 USPQ at 326-27.

In the patent context, not all functional descriptions of genetic material necessarily fail as a matter of law to meet the written description requirement; rather, the requirement may be satisfied if, in the knowledge of the art, the disclosed function is sufficiently correlated to a particular, known structure. (*Amgen v. Hoechst Marion Roussel* 314 F.3d 1313 Fed.Cir. 2003).

Claims 1 and 10, as amended, recite that the organisms are genetically engineered to express genes that encode a diol oxidoreductase or aldehyde dehydrogenase, which are active in bacteria or plants. Support for this amendment can be found, for example, on page 5, line 18 to page 6, line 28. Claim 8, as amended, recites that the organism expresses genes that encode diol oxidoreductase and aldehyde dehydrogenase. The claims now require that the genetically engineered organisms express a form of a diol oxidoreductase or aldehyde dehydrogenase that is functional in bacteria or plants. This should overcome the Examiner's allegations that the claims are drawn to genera of enzymes having any structure. The claimed genes and enzymes were well known to those skilled in the art, commercially available and sufficiently identified in the specification as of the date of filing to reasonably convey to one skilled in the art that the inventors had possession of the claimed invention.

As affirmed by the Court in *Spectra-Physics, Inc. v. Coherent, Inc.*, 827 F.2d 1524 (Fed. Cir. 1987), a patent need not teach, and preferably omits, what is well known in the art. The publications cited in the specification (page 6, lines 3-28), submitted with the IDS (Skraly et al.

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*Appl. Environ. Microbiol.* 64:98-105 (1998); Daniel et al. *J. Bacteriol.* 177(8) 2151-2156 (1995)), and enclosed with this response (Leurs et al. *FEMS Microbiol. Lett.* 154(2): 337-345 (1997); Tong et al. *Appl. Environ. Microbiol.* 57(12):3541-3546 (1991); Yoshida et al. *Eur. J. Biochem.* 251:549-557 (1998) and op den Camp et al. *Plant Mol. Biol.* 35(3): 355-365 (1997)) demonstrate that the genes and enzymes can be obtained from a number of organisms and that sequence information for both aldehyde dehydrogenase and diol oxidoreductase were well known in the art as of the priority date of this application, July 21, 2000. The publications also show that the enzymes are active in bacteria and plants. Furthermore, actual DNA can be obtained from the authors of the publications or purchased from commercial suppliers, such as the American Type Culture Collection (ATCC). Published amino acid and nucleotide sequence listings for the various genes can also be obtained from GenBank or the National Center for Biotechnology Information (NCBI).

In addition to those nucleic acid sequences defined as specific *aldH* and *dhaT* genes in the specification, the primer and/or oligonucleotide sequences used to hybridize to, and isolate, those sequences can be used to isolate other genes encoding the claimed enzymes. This is routine to those skilled in the art. For example, the specification states that the *aldH* gene was cloned by PCR from the *E. coli* genome on the basis of its homology with other aldehyde dehydrogenases (Example 1 and specifically, page 9, lines 29-30). Therefore, the same technique can be used to isolate aldehyde dehydrogenase from other organisms, and the process can be repeated to isolate diol oxidoreductases. The methods in which one of ordinary skill in the art would use to isolate the claimed genes lie at the very heart of defining the structural

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nature of each gene. The structures of the claimed genes are clearly limited based, in part, on the requirement for them to be complementary to the primers and/or oligos disclosed, for example, in Example 1.

Furthermore, it was well known that a number of different organisms have the cellular machinery to produce polyhydroxyalkanoates, either endogenously, or through genetic engineering. For example, Madison and Huisman *Microbiol. Mol. Biol. Rev.* 63(1): 21-53 (1999), which is recited in the specification on page 4, lines 1-2, discusses the production of polyhydroxyalkanoates in bacteria (pages 37-40 and 41-44) and other microorganisms (pages 40-41), yeast (page 44), plants (page 45), insect cells (page 45), and animal tissues (page 45). Therefore, it is clear that the applicants were in possession of a wide range of species that could be used in the claimed methods and systems.

Finally, the Examiner alleges that the claims are drawn to a genus of any diols. This is not correct. The claims are directed to a method or system where an organism can convert diols into 4-hydroxybutyrate, 2-hydroxybutyrate, 4-hydroxyvalerate, 5-hydroxyvalerate, 6-hydroxyhexanoate, 2-hydroxyethanoate, 2-hydroxypropionate, or 3-hydroxyhexanoate monomers. Therefore, the claims are not directed to *any* diols; the claims are directed to diols which lead to the production of specific hydroxyalkanoate monomers.

**Rejection Under 35 U.S.C. § 112, first paragraph (enablement)**

Claims 1-4 and 6-10 were rejected under 35 U.S.C. § 112, first paragraph, as not being enabled. Applicant respectfully traverses this rejection to the extent that it is applied to the claims as amended.

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The Court of Appeals for the Federal Circuit (CAFC) described the legal standard for enablement under 35 U.S.C. § 112, first paragraph, as whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art, without undue experimentation ( *See, e.g., Genentech, Inc. v. Novo Nordisk A/S*, 108 F.3d at 165, 42 USPQ2d at 1004 (quoting *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *See also In re Fisher*, 427 F.2d at 839, 166 USPQ at 24; *United States v. Telectronics, Inc.*, 857 F.2d 778 (Fed. Cir. 1988); *In re Stephens*, 529 F.2d 1343 (CCPA 1976)). The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation (*M.I.T. v. A.B. Fortia*, 774 F.2d 1104 (Fed. Cir. 1985)). In addition, as affirmed by the Court in *Spectra-Physics, Inc. v. Coherent, Inc.*, 827 F.2d 1524 (Fed. Cir. 1987), a patent need not teach, and preferably omits, what is well known in the art.

Whether the disclosure is enabling is a legal conclusion based upon several underlying factual inquiries. *See In re Wands*, 858 F.2d 731, 735, 736-737, 8 USPQ2d 1400, 1402, 1404 (Fed. Cir. 1988). As set forth in *Wands*, the factors to be considered in determining whether a claimed invention is enabled throughout its scope without undue experimentation include the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claims. In cases that involve unpredictable factors, "the scope of the enablement obviously varies inversely with the degree of unpredictability of the factors involved." *In re*

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*Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The fact that some experimentation is necessary does not preclude enablement; what is required is that the amount of experimentation 'must not be unduly extensive.' *Atlas Powder Co., v. E.I. DuPont De Nemours & Co.*, 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir. 1984). There is no requirement for examples.

A proper analysis of the *Wands* factors shows that the claims satisfy the enablement requirement. The courts have indicated that some experimentation is permitted as long as such experimentation is not undue. As stated in *MIT v. A.B. Fortia*, "The fact that experimentation may be complex does not make it undue if the art typically engages in such experimentation". It clear from the amount of direction or guidance presented in the specification, the presence of working examples, the state of the prior art, and the relative skill in the art that one of ordinary skill in the art would be able to make and use the claimed genetically engineered organisms for the production of polyhydroxyalkanoates without undue experimentation.

As discussed above, the specification and the prior art disclose organisms that can be genetically engineered to produce PHAs (page 5, lines 18-21), diols that may be utilized to form the claimed hydroxyhexanoate monomers (page 9, lines 15-25), and organisms from which diol oxidoreductase and aldehyde dehydrogenase genes have been isolated and how to obtain these genes and enzymes (page 6, lines 2-28; Example 1). In addition, Applicants have two issued patents, U.S. Patent No. 6,329,183 and U.S. Patent No. 6,576,450, with claims directed to the production of PHA's by providing diols to genetically engineered organisms (although the patents do not disclose the claimed subject matter). Once a gene is identified, it is routine in the

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art to incorporate the gene into a plasmid for expression in cells. There is sufficient direction and guidance given by the specification to construct plasmids and express the claimed genes (see Examples). In addition, the experimental protocols are routine in the art and expression vectors, restriction enzymes and ligation enzymes are also commercially available.

Although there is no requirement for examples, Applicants have provided numerous working examples which not only demonstrate that one can use the claimed enzymes to engineer organisms to produce polyhydroxyalkanoates from diols, such as 1,4-butanediol (Examples 3, 4 and 7; 1,3-propanediol (Examples 5 and 6), but that one can isolate the desired enzymes with only routine experimentation. For instance, Example 1 discusses a standard method for cloning the *aldH* gene from the *E. coli* genome using PCR, and Heim and Strehler. *Gene* 99(1):15-23 (1991) (abstract enclosed) demonstrates the cloning of an *E. coli* gene encoding an ALDH, remarkably similar to mammalian aldehyde dehydrogenases, in 1991! Similar methods can be used to clone diol oxidoreductase genes and would be routine to one of skill in the art as of the July 21, 2000 priority date of this application.

Furthermore, the enzymes may be selected based on their substrate specificity. As discussed at page 6, lines 24-28, of the specification, "The choice of an appropriate aldehyde dehydrogenase for use in metabolic engineering should be done after evaluation of the substrate specificity of several candidates. Enzyme assays such as that described in Baldom & Aguilar (1987, J. Biol. Chem. 262:13991-6) are useful for such diagnoses." The substrate, in the presence of its cognate active enzyme, will be readily converted into product. Based upon the specification, the cited reference, and the Examples one of ordinary skill in the art will appreciate

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that assays for enzyme specificity and the presence, or production, of end-product (i.e. polyhydroxyhexanoate) is easily measured and characterized.

**Rejection Under 35 U.S.C. § 112, second paragraph**

Claim 8 was rejected under 35 U.S.C. § 112, second paragraph, as being indefinite.

Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

Claim 8 has been amended to recite that the organism expresses genes which encode aldehyde dehydrogenase and diol oxidoreductase. This amendment is clearly supported by the specification, for example, on page 6, lines 3-28; and Examples 1 and 2.

**Claim Objections**

Claim 8 was objected to for reciting abbreviations. Applicants respectfully traverse this objection to the extent that it is applied to the claims as amended.

The amendment to claim 8 stated above should overcome this rejection.

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Allowance of claims 1-4 and 6-10, as amended, is respectfully solicited.

Respectfully submitted,



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